A laparoscopic swine model of noncompressible torso hemorrhage

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BACKGROUND: Hemorrhage persists as the leading cause of potentially preventable civilian and military death. Noncompressible torso hemorrhage (NCTH) is a particularly lethal injury complex, with few contemporary prehospital interventions available. Various porcine models of hemorrhage have been developed for civilian and military trauma research. However, the predominant contemporary models lack key physiologic characteristics including the natural tamponade provided by an intact abdominal wall.

To improve physiologic and clinical relevance, we developed a laparoscopic model of NCTH. This approach maintains both the integrity of the peritoneum and the natural tamponade effect of an intact abdominal wall while preserving the intrinsic physiologic responses to hemorrhage. Furthermore, we present data quantifying the contribution of the swine contractile spleen in the context of uncontrolled hemorrhage.

METHODS: Anesthetized adult male Yorkshire swine underwent a laparoscopic Grade V liver injury, with or without open preinjury splenectomy. Animals were observed without intervention for a total of 120 minutes after injury to simulate point of injury, transport time, and arrival at hospital.

RESULTS: Shed blood to body weight ratio did not differ among groups; however, mortality was higher in splenectomized animals (67% vs. 33%). Cox regression modeling demonstrated a critical time point of 45 minutes and blood pressure as significant predictors of mortality.

CONCLUSION: This study describes a model of NCTH that reflects clinically relevant physiology in trauma and uncontrolled hemorrhage. In addition, it quantitatively assesses the role of the swine contractile spleen in the described model. (*J Trauma Acute Care Surg*. 2014;77: S77 S82. Copyright © 2014 by Lippincott Williams & Wilkins)

KEY WORDS: Noncompressible torso hemorrhage; splenectomy; swine.

Hemorrhage remains the leading cause of preventable mortality from both civilian and military traumatic injury,[1–3] with the majority of deaths occurring in the prehospital phase of care.[3–5] The prehospital management of hemorrhage originating from compressible sites (i.e., extremity) has seen the rapid translation of concepts explored in animal models of compressible hemorrhage to clinical application with a resultant mortality reduction. However, noncompressible torso hemorrhage (NCTH), despite being particularly lethal,[6–9] has not seen the same level of consideration in experimental design and animal modeling.

Crucial to the development of prehospital adjuncts for NCTH is the development of animal models that predictably reflect the lethality of NCTH. Swine have consistently demonstrated utility as an animal model of injury.[10–14] They exhibit a similar physiologic response to hemorrhage compared with humans, along with similarities in torso anatomy, with the exception of a contractile spleen. The swine spleen permits swine the ability to autotransfuse a volume of red blood cells amounting up to 22% of their total erythrocyte content (although not considered to contribute to normophysiologic hemodynamics).[15] This physiologic difference needs to be reconciled when planning studies that involve this species.

A common approach in swine for uncontrolled hemorrhage has been the open (midline) laparotomy facilitating organ injury (most commonly a liver crush or spleen incision).[10,11] Traditional models permit for study convenience such as the ability to continuously monitor hemorrhage volume. However, we are keenly aware that many pathways contribute to the physiologic response to trauma—cardiovascular response, abdominal wall and visceral tamponade, coagulation and inflammatory pathways—which are often not represented in toto.

The purpose of this study was to describe a method of laparoscopic liver injury to produce a model of uncontrolled NCTH. The aim was to develop a model that preserves important anatomic and physiologic relationships permitting a

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The experiments reported herein were conducted in compliance with the Animal Welfare Act and in accordance with the principles set forth in the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animals Resources, National Research Council, National Academy Press, 1996.

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true characterization of the response to injury. In addition, within this model, the role of the contractile spleen was evaluated quantitatively to determine the effect of autotransfusion on uncontrolled hemorrhage model performance and outcomes. The authors hypothesized the following: (1) that a laparoscopic approach to NCTH preserving the abdominal wall anatomy is feasible and will result in a robust model for civilian and military NCTH studies and (2) that swine undergoing splenectomy will exhibit reduced survival as compared with their experimental counterparts where the spleen is left intact.

MATERIALS AND METHODS

Study Overview

Institutional animal care and use protocol review and approval was obtained for the study described herein. All studies were performed at the Tri-Service Research Laboratory at Fort Sam Houston, Texas, an Association for Assessment and Accreditation of Laboratory Animal Care–accredited facility. Animals were treated in accordance with the *Guide for the Care and Use of Laboratory Animals*. Upon arrival, animals were housed for 7 days before their use in experimental protocols for quarantine and acclimation.

Male, Yorkshire swine (*Sus scrofa*; weight range, 50–73 kg) were used to study the effect of a laparoscopic liver injury on animal physiology, biochemistry, and mortality. The study consisted of two groups as follows: swine with spleen (spleen group, n = 12) and swine without spleens (splenectomy group, n = 12). The study was executed in four phases: animal preparation, surgery, injury, and observation phases.

Animal Preparation

Swine were anesthetized, intubated, and instrumented for physiologic telemetry (i.e., rectal temperature, end-tidal carbon dioxide, continuous pulse oximetry, invasive arterial pressures) and placed in dorsal recumbency. A left inguinal incision was performed, a portion of the adductor muscle was removed, and the femoral vessels were identified. The femoral artery was instrumented using a small catheter (Harvard Apparatus, Holliston, MA), the femoral vein was instrumented with a 7 Fr angiocatheter (BD Medical, Franklin Lakes, NJ), and the skin was reapproximated using staples.

Surgery

The swine that did not receive a splenectomy underwent laparoscopic port placement using a Hassan technique, which involved a small cut down into the peritoneal cavity, immediately cranial to the umbilicus. Under direct vision, an 11-mm laparoscopic port (Endo-Ethicon, Johnson & Johnson, New Brunswick, NJ) was sutured into place. Two additional 11-mm ports were placed lateral to the third and fourth nipple interspaces of their respective sides. A 5-mm port was placed medially to the right third/fourth nipple interspaces (Fig. 1).

In the splenectomy group only, a midline laparotomy was performed extending from the xiphoid process to just the inferior of the urethral meatus. An orogastric tube was inserted and manually positioned in the antrum of the stomach to decompress the gastric contents. A splenectomy was then performed as follows.

The cranial portion of the spleen is mobile and was delivered into the midline. The omental ligaments were taken down using diathermy, until a vascular pedicle was encountered, which was divided between Kockers clamps and ligated with 1'0 silk. Mobilization of the spleen was continued by dividing the omentum close to the spleen. The mobilization of the superior splenic pole was accomplished by dividing the gastrosplenic ligament, taking care to ensure hemostasis of the short gastric vessels. The remainder of the spleen was mobilized by diving the remaining one or two vascular pedicles that were associated with the inferior pole of the spleen. Throughout the procedure, care was taken to ensure that the integrity of the visceral peritoneum and immaculate hemostasis

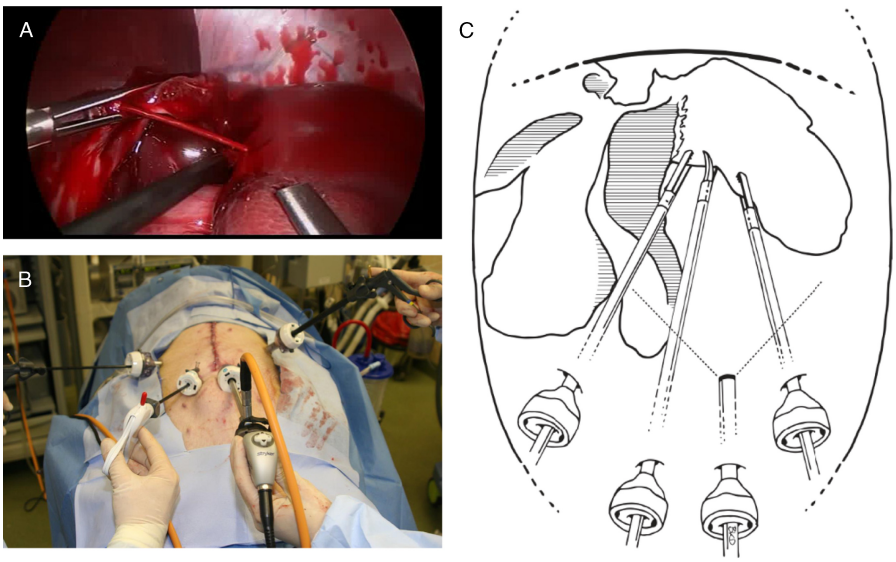

Figure 1. *A*, Operative procedure. *B*, Laparoscopic view. *C*, Operative view. Line drawing demonstrating port and instrument placement and optimal approach to the transection.

were maintained. After removal, the spleen was weighed, draped in a normal saline–soaked laparotomy sponge, and stored in a fluid warming cabinet. The warmed spleen was placed back into the abdominal cavity in its normal anatomic position to avoid the creation of an abdominal void where blood might pool abnormally and affect abdominal tamponade and hematoma formation at the injury site.

Injury

The central lobe of the liver was retracted laterally, helping to display the left lobe, which was delivered into the operative field by hand in the splenectomy group or by Babcock grasper in the nonsplenectomized group (Fig. 1). The left lobe was measured at the maximum *x*-axis and *y*-axis and then carefully marked along a projected line of transection with Bovie electrosurgery that would enable an approximately 80% resection. The liver was returned to its normal anatomic position. In the splenectomy group, laparoscopic ports were placed under direct visualization with positioning as described earlier. The peritoneum was closed with 2-0 vicryl suture in a continuous fashion, and the midline fascia layer was closed with 2-0 polydioxanone suture in a continuous fashion. The skin was reapproximated using staples.

The swine were then placed in the reverse Trendelenburg position, and a pneumoperitoneum was established by insufflation with carbon dioxide (15 mm Hg). Following visualization with a laparoscope, an atraumatic grasper (left port) was used to retract the central lobe, with a further grasper retracting the left lobe (right port) (Fig. 1). The liver parenchyma was then divided along the marked line with endosheers. After the completion of the liver transection, the operating table was leveled, the abdomen was allowed to fully desufflate, all ports were removed, and incisions were rapidly closed with skin staples.

Observation

The initiation of liver injury was designated as $T = 0$. The animals were naïve to fluid resuscitation and no postinjury interventions were performed. Total observation time before euthanasia was $T = 120$ minutes, designated as within the outer limits of transport time at which a casualty might arrive at a facility for surgical intervention.

Data Collection and Study End Points

Whole arterial and venous blood was sampled at the following time points: (1) before splenectomy procedure, (2) baseline ($T = 0$ minute) to immediately before liver transaction, and (3) $T = 10$, 20, 30, 45, 60, 75, 90, 105, and 120 minutes. Venous and arterial blood gas and chemistry was assayed using an ABL-837 (Radiometer, Copenhagen, Denmark).

At the time of death or euthanasia, a laparotomy was performed. Shed blood and blood clots were collected by suction or manual removal, placed into preweighed basins and weighed. Unclotted blood and clotted blood weights were combined to determine total shed blood volume by weight.

Statistical Analysis

All continuous variables are summarized by mean (SD), and categorical variables are summarized by frequencies (percentage). Univariate comparison of baseline values were performed using *t* tests for continuous variables and χ^2 for ordinal data. The primary outcome of time to death was assessed using a Cox regression model, with adjustment for treatment group, biomarker, and the interaction of time. Each biomarker of interest was modeled independently to assess their association with treatment and their impact on survival. Statistical analyses were performed using SAS version 9.3 (Cary, NC).

RESULTS

Baseline and Injury Characteristics

The study used a total of 24 animals divided equally into the spleen and splenectomy groups (Table 1). Because of the sequential execution of experimental groups and the unavailability of larger specimens for the splenectomy arm, the animals in the spleen group were significantly heavier (kg) than those in the splenectomy group (66.7 [3.4] vs. 58.4 [5.6], $p < 0.001$). Preinjury baseline mean arterial pressure (MAP), pH, lactate, and base excess measurements were similar between the groups ($p > 0.05$). The preinjury heart rate was higher in the splenectomy group than in the spleen group (104 [30] vs. 69 [9], $p = 0.002$).

Both groups achieved the desired percentage by weight resection of the left lateral liver lobe (82 [10] and 80 [5] for the spleen and splenectomy groups, respectively; $p = 0.178$). This resulted in a consistent total hemorrhage (mL) between the groups, with 1,907 (684) collected from the spleen group and 1,257 (206) from the splenectomy group. When normalized for weight (mL/kg), this translated to 29 (11) and 22 (4), respectively ($p = 0.242$) (Table 2).

Cardiovascular and Metabolic Response to Hemorrhage

Both groups underwent a similar precipitous fall in systolic blood pressure (SBP) immediately after injury with similar pressures for both the spleen and splenectomy groups (39.1 [15.6] and 36.0 [16.8], respectively; $p = 0.96$) (Fig. 2*A*). Both groups subsequently recovered their pressures, although the spleen group demonstrated a stronger recovery, rising to a peak SBP of 69.8 (16.8) at 70 minutes. These animals then

TABLE 1. Baseline Characteristics of the Study Groups

Parameter	Spleen	Splenectomy	*p*
n	12	12	
Weight, kg	66.7 ± 3.4	58.4 ± 5.6	<0.001
Male	12 (100%)	12 (100%)	n/a
MAP, mm Hg	61 ± 6	64 ± 9	0.300
Heart rate, beats/min	69 ± 9	104 ± 30	0.002
pH	7.426 ± 0.426	7.407 ± 0.128	0.646
Lactate, mmol/L	1.9 ± 0.5	1.6 ± 0.8	0.430
Base excess	4.8 ± 4.2	3.2 ± 4.4	0.397
Total blood volume	4,467 ± 229	3,914 ± 374	0.001
Shed blood	1,907 ± 684	1,257 ± 206	0.052
Shed blood/weight	29 ± 11	22 ± 4	0.242
Shed blood/total blood volume, %	43 ± 16	32 ± 5	0.242
Liver injury, %	82 ± 10	80 ± 5	0.178

Values are displayed as mean ± SEM.

TABLE 2. Hazard Ratios for Clinical Variables

	HR	95% CI	*p*
SBP	0.88	(0.80 0.97)	0.008
DBP	0.88	(0.80 0.96)	0.004
HR	0.98	(0.97 1.00)	0.020
MAP	0.87	(0.78 0.96)	0.004
LAC	1.08	(0.93 1.24)	0.310
BE	0.95	(0.88 1.02)	0.130
pH	1.15	(0.70 1.90)	0.580
Hct	0.98	(0.74 1.30)	0.910

Modeled with adjustment for treatment, variable measure, and time dependency (>45 minutes specified). BE, base excess; CI, confidence interval; DBP, diastolic blood pressure; Hct, hematocrit; HR, heart rate; LAC, lactate; SBP, systolic blood pressure.

maintained a plateau SBP between 68 and 72 for the remainder of the experiment. Animals in the splenectomy group achieved a more modest recovery of their SBP to a maximum value of 56.7 (7.6) at 70 minutes. This was followed by labile pattern for the remainder of the experimental period, descending as low as 44.5 (14.1) at 110 minutes.

The trend in lactate measurements across the groups also differed (Fig. 2*B*). While both groups see an initial rise, this slows in the spleen group to a maximum value at the end of study of 4.7 (3.2). This is in contrast to the splenectomy group, which sees a maximum value of 9.9 (2.2) at 105 minutes.

Mortality Analysis

At the end of the study (120 minutes), there were four deaths in the spleen group and eight within the splenectomy group ($p = 0.22$). All of the deaths within the spleen group occurred within the first hour (20, 25, 30, and 50 minutes). Of the eight deaths in the splenectomy group, five occurred within the first hour (25, 30, 35, 45, and 45 minutes) and the remaining three at 110 minutes each (Fig. 3). Splenectomy doubled overall mortality at 2 hours from 4 (25%) to 8 (75%) of 12. Cox regression modeling identified a significant increase in cumulative hazard for death in the splenectomy compared with the spleen group at 45 minutes (Fig. 4*A*). Following the inclusion of the collected cardiovascular and metabolic parameters, blood pressure was identified as the most significant predictor of outcome (Fig. 4*B*, Table 2).

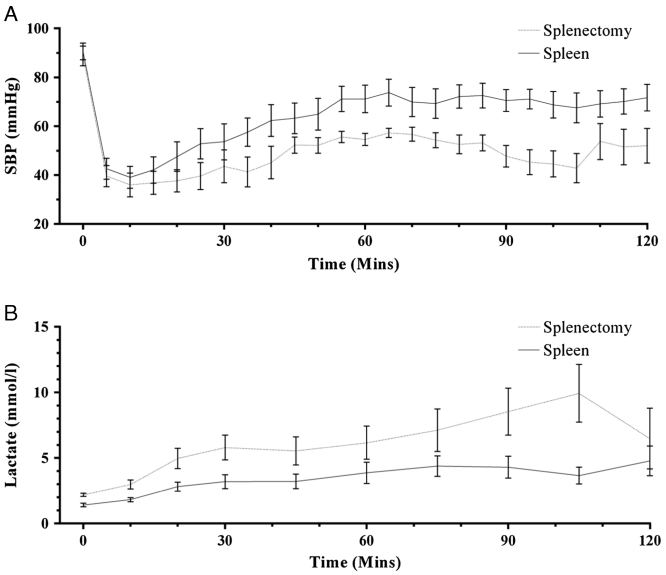

Figure 2. SBP (*A*) and lactate (*B*) measurement trends throughout the experimental time course.

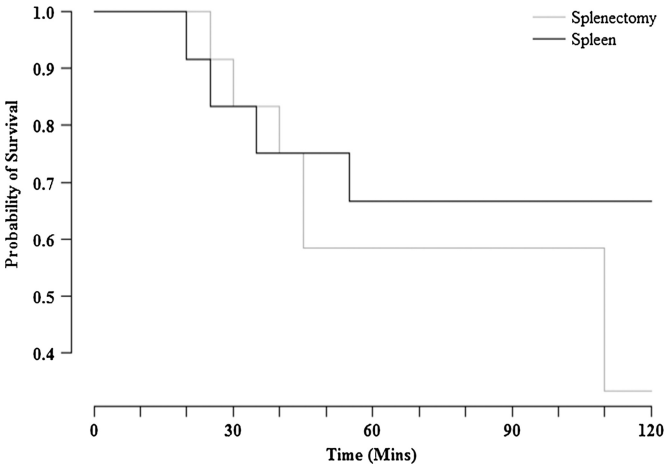

Figure 3. Kaplan-Meier survival curve.

DISCUSSION

This work describes a novel approach to NCTH modeling in swine that reflects civilian- and battlefield-relevant hemorrhagic pathology with the ensuing physiologic sequelae. In addition, this is the first swine hemorrhage model that quantitatively characterizes the contribution of the contractile spleen to survival and physiologic outcomes. In the described model, animals without a spleen were more likely to die, with 45 minutes after injury identified as a critical time point aligning with current reports of prehospital death caused by NCTH. By characterizing the contribution of the contractile spleen in this model, we have identified an approach to manipulating the timing and rate of mortality. Furthermore, the strongest predictor of outcome was blood pressure and, although not a new finding, highlights the importance of this parameter in NCTH.

The last decade of war has driven a resurgence of interest in NCTH because of the high mortality of this injury type. In an analysis of 10 years of US military combat deaths, Eastridge et al.[3] identified 976 potentially survivable casualties from a cohort of 40,16. A peer review process identified torso hemorrhage as the leading cause of death in 598 fatalities. NCTH has since been examined in greater detail by investigators using both the US and UK military trauma registries.[7,9] Axial vessel disruption and pulmonary injury have been consistently identified as the most lethal foci of torso hemorrhage on the battlefield, with an overall mortality between 18.7% and 41.9%. Interestingly, this is also the pattern observed in civilian practice; Kisat et al.[6] used the US National Trauma Data Bank to demonstrate a mortality of 44.6%. The odds ratio of death for vessel disruption

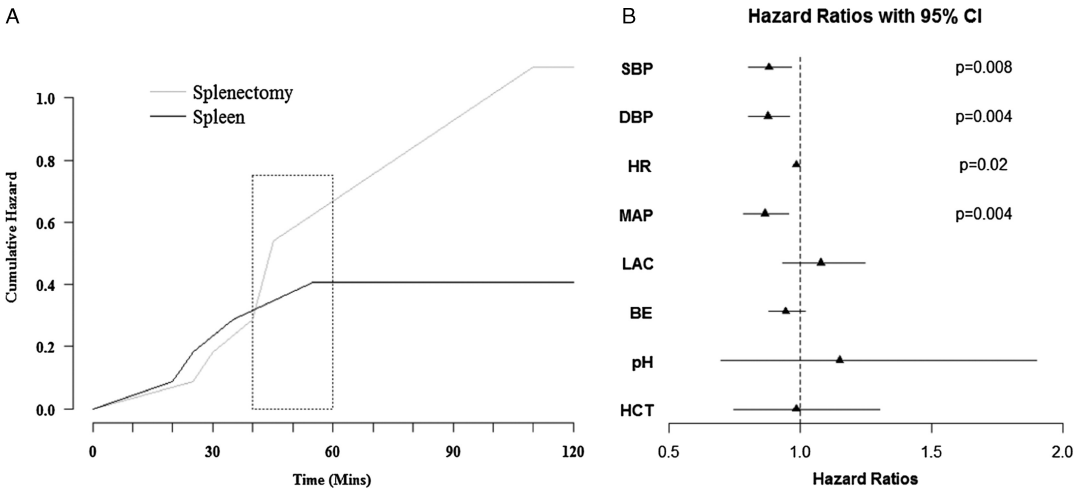

Figure 4. *A*, Cumulative hazards by treatment group. *B*, Hazard ratios for physiologic parameters. Hazard ratios are displayed with their respective 95% C.

and pulmonary injury was 1.54 (95% confidence interval, 1.33–1.78) and 1.32 (95% confidence interval, 1.18–1.48), respectively.

The current study extends the body of literature regarding the genesis of NCTH models in translational research. The most well-established solid organ hemorrhage models are liver,[11] owing to its large size and vascular nature, and spleen, a more perplexing organ of choice considering its poor anatomic homology to the human organ.[16] The earliest such investigations into hemorrhagic or surgical shock in large animals can be traced back to the late 1800s and early 1900s.[17,18] The approach and methodologies for hemorrhagic shock models have transformed throughout the last century. These have evolved into contemporary models as established at institutions such as the US Army Institute of Surgical Research, Naval Medical Research Center, and various collaborating academic institutions.[10–12,19]

The exciting evolution of surgical technology, in the form of laparoscopy, has now enabled minimal access animal models of uncontrolled hemorrhage and resuscitation. This study is the first description of a laparoscopic approach to NCTH and is a progression of the more common approach of the open laparotomy and crush, laceration, or incision of a solid organ.[10,11] While other models have achieved similar injury patterns with uncontrolled hemorrhage using wires placed around named vessels or visceral structures,[20–22] the advantage of the laparoscopic approach is multifold. The induction of the solid organ injury through the direct visualization afforded by laparoscopy allows for better standardization, as evidenced by the postexperiment evaluation of liver transection. The insertion of laparoscopic ports, in the presence or absence of a midline laparotomy, simulates the soft tissue injury expected in penetrating wounds from various projectiles and is easily standardized because of the port diameter and consistency of anatomic placement.

The current study has limitations. The surgical complexity of this study, despite its reproducibility, requires a degree of surgical competency in both open and laparoscopic techniques. It is of note, however, that the majority of the procedures described within were accomplished by nonclinical personnel. It is the expectation of the authors that eventually, the splenectomy can also be performed laparoscopically. Pilot studies are underway to develop a laparoscopic functional splenectomy, thereby eliminating the soft tissue trauma incurred at laparotomy with an open approach.

In addition, the 2-hour postinjury time point covers only transport to hospital timelines and does not include any attempt at definitive surgical or critical care. We have now completed studies using this model that integrate a more robust "in-hospital" phase where surgical control of hemorrhage is achieved and contemporary damage control resuscitation is provided.[23] The authors recognize that because of the sequential nature of the development of this model and therefore the lack of spleen and splenectomy group randomization, differing animal group weights and different surgical preparation may have influenced the interpretation of the spleen's effect on survival. Even in light of these limitations, we expect that this model will be effectively adapted for use in the investigation of both mechanical and pharmacologic interventions targeting NCTH.[24,25] Lastly, it is important to recognize that while this model achieves the intent of the investigators, to provide a platform for NCTH intervention research and training, it does not necessarily reflect all clinical presentations of NCTH. Therefore, mortality outcomes in research using this model should be interpreted with caution and proper clinical context.

CONCLUSION

We have demonstrated that physiologic, battlefield, and civilian clinical relevance can be achieved in a large animal model of uncontrolled, noncompressible, hemorrhage, in particular, time to prehospital death. We also provide quantitative evidence that the swine contractile spleen holds important influence, which should be considered when planning hemorrhage studies using this model. While this model in no way attempts to replace all large animal hemorrhage models, it can serve as a "hub" for multiple "spoke" investigations into NCTH interventions

and prehospital resuscitation strategies, particularly with the addition of definitive surgical intervention and critical care phases to the experimental protocol.

AUTHORSHIP

J.D.R. and C.J.B. share equal contribution to manuscript and first au thorship. J.D.R. and C.J.B. conceived and managed the study, execution of experiments, data analysis and manuscript authorship. E.M.S. exe cuted the experiments, collected and analyzed the data, editorial con tribution to manuscript. L.A.Z. performed statistical analysis of data, construction of figures and tables and editorial contribution to manu script; J.J.M. executed the experiments and analyzed the data.

DISCLOSURE

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